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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/497,591	02/03/2000	Gary L. Nelsestuen	09531-016001	7689

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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/497,591	NELSESTUEN, GARY L.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *76-86* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *76-86* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 14, 2003 has been entered.

Status of the Claims

The amendment filed April 14, 2003 has been entered. Claims 1-75 have been cancelled and Claims 76-86 have been added. Therefore, Claims 76-86 are pending and have been considered on the merits in this Office Action.

Objections/Rejections Withdrawn

The objection to the Specification for failing to comply with the sequence rules is withdrawn in light of Applicants response (see p. 5 of Paper No. 20).

The objection to Claims 8, 73, 74, and 75 is withdrawn in light of the amendment.

The rejection of Claims 9-14 under 35 U.S.C. 112, second paragraph, as being indefinite as to failing to provide a reference point for an amino acid substitution is withdrawn in light of the amendment.

The rejection of Claims 8, 61-63 and 75 under 35 U.S.C. 112, first paragraph is withdrawn in light of the amendment and response (p. 6 of Paper No. 20).

The objection of Claims 67-72 as being substantial duplicates of claims 61-66 is withdrawn in light of the amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 76-86 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 76-86 are indefinite because Claims 76, 79, and 86 recite "effective amount" of protein C or activated protein C without providing what effect the protein C is intended to have so that one could determine when the amount is "effective". Dependent claims do not clarify this ambiguity and are therefore also rejected.

Priority

It is noted that the present claims have not been given the priority date of the parent applications. The present Application is a CIP of application numbers 09/302,239 and 08/955,636. The parent applications only disclose methods of treatment wherein protein C is used in place of aspirin, warfarin, and heparin and not in combination with these anticoagulant agents. Therefore, for prior art determinations, the actual filing date of 02/03/00 has been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 76, 77, and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smirnov et al. (U.S. Patent No. 5,837,843).

Smirnov et al. teaches a human protein C polypeptide wherein the human protein C Gla domain sequence has been replaced with the prothrombin Gla domain. The modified Gla domain taught in Smirnov et al. contains amino acid substitutions at positions 10, 11, 28, 32, and 33 as compared to SEQ ID NO:1 of the present application (see SEQ ID NO:1 of Smirnov et al. which is the prothrombin Gla domain sequence). Smirnov et al. teaches that the modified activated protein C exhibits much higher anticoagulant activity than unmodified activated protein C (Col. 10, lines 35-43).

Smirnov et al. also states that the modified protein C is less sensitive to inhibition by natural inhibitors of protein C and does not need the same cofactors to be effective in patients with lowered levels of the cofactors such as protein S or the lipids present in activated platelets (see abstract). Smirnov et al. describes the dose and administration of the modified protein C in methods of treatment (Col. 5, lines 15-30). Smirnov et al. does not present a specific protocol for the administration of the disclosed modified protein C and an anticoagulant. However, Smirnov et al. suggests that since the modified protein C optimal activity does not depend on normal levels of protein S, it could be used in the treatment of conditions wherein the patient's protein S is low such as in conditions during warfarin coagulation(see Col. 5, lines 30-47). (Treatment with the oral anticoagulant, warfarin, reduces levels of both protein C and protein S). Thus, Smirnov et al. implies that the modified protein C described therein can be used in combination with warfarin in a method of treatment.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the modified protein C polypeptide described in Smirnov et al. in a method of treatment comprising administering the modified protein C polypeptide of Smirnov et al. and the anticoagulant agent, warfarin because Smirnov et al. suggest doing so (Col. 5, lines 31-50). One of ordinary skill in the art would have had a reasonable expectation of success in such a method because Smirnov et al. teaches that the modified protein C has higher anticoagulant activity than unmodified protein C and does not need the same cofactors to be effective in patients with lowered levels of

those cofactors (such as lowered protein S during Warfarin treatment) (see abstract). Thus, the claims are unpatentable over Smirnov et al.

Claims 76-86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wakako et al. (EP 0 296 413; ref. AM of IDS) in view of Grinnell et al. (U.S. Patent No. 6,071,514; reference AB of IDS of Paper No. 21).

Wakako et al. teach a human protein C wherein the Gla domain is replaced by the Gla domain of factor X resulting in a chimeric protein with more potent anticoagulation activity than the wild-type human protein C (see p. 2, lines 35-40 and p. 9, lines 25-30). The substituted Gla domain contains substitutions at positions 10, 11, 28, 32, and 33 with respect to SEQ ID NO:1 of the present invention and contains a glycine at residue 11, a glutamate at residue 32, and an aspartate at residue 33 (see Table 1). Wakako et al. imply that the disclosed hybrid proteins are to be used in methods of treating blood clots (p. 3, lines 34-35).

Wakako et al. do not specifically disclose a method of treatment comprising administering the disclosed protein C and an anticoagulant agent.

Grinnell et al. disclose a combination therapy with human activated protein C and antiplatelet (anticoagulant) agents such as aspirin and heparin (see abstract). Grinnell et al. teach that the combination of activated protein C and antiplatelet (anticoagulant) agents results in a synergy that will allow the reduction of the dosages of both activated protein C and the antiplatelet agents (Col. 2, lines 17-20).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use the protein C polypeptides having a modified Gla domain as described in Wakako et al. in combination with the anticoagulants, aspirin and/or heparin in a method of treatment as described in Grinnell et al. One of ordinary skill would recognize from Grinnell et al. the need for reduced dosages of protein C and anticoagulants and the success of treatment using protein C combined with an anticoagulant. And, with Wakako et al. in hand, the artisan of ordinary skill would recognize the that the method of Grinnell et al. could be improved by using a more potently active protein C polypeptide such as that described in Wakako et al. One of ordinary skill at the time of the invention would have a reasonable expectation of success since Grinnell et al. show that the combination of activated protein C and aspirin results in a significantly greater inhibition of thrombus formation than with activated protein C alone and since Grinnell et al. conclude from their studies that patients treated with activated protein C combined with antiplatelet agents such as aspirin or heparin will achieve increased efficacy and that therapeutic doses of activated protein C may be reduced in the presence of anti-platelet therapy (see Example 1, especially Col. 8, lines 5-55). With the teachings of Wakako et al., one of ordinary skill at the time of the invention, would have recognized that substituting the protein C used in Grinnell et al. with the modified protein C of Wakako et al. would have allowed an even greater reduction in the therapeutic doses of protein C necessary since Wakako et al. teach that the protein disclosed therein has more potent anti-coagulation activity. Thus, the claims are unpatentable over Wakako et al. in view of Grinnell et al.

Conclusions

No Claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703)

308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

HS

Holly Schnizer
May 14, 2003

Christopher S.F. Low

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